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10/520,436	08/17/2006	Sarah Kingsland	FDEHN7.002APC	5916

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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
11/25/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/520,436	KINGSLAND ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,16-20 and 22-34* is/are pending in the application.

4a) Of the above claim(s) *16-20,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5 and 24-33* is/are rejected.

7)☒ Claim(s) *34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/11/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 11, 2009 has been entered.

2. Claims 1, 3-5, 16-20 and 22-34 are pending.

3. Claims 16-20, 22 and 23 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1, 3-5 and 24-34, drawn to a method for separation and purification of fibrinogen and plasminogen, are being acted upon in this Office Action.

5. The rejection of claims 1, 3-5 and 24-27 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01 has been obviated by the claims amendment filed September 11, 2009.

6. The rejection of claim 11 under 35 U.S.C. 102(b) as being anticipated by WO 95/25748 publication (published Sept 1995; PTO 1449) has been obviated by the claims amendment filed September 11, 2009.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. **This is New Matter**.

The recitation of "buffers for eluting plasminogen **and**/or fibrinogen comprises a salt of citrate, phosphate **or** chloride" for the claimed method in claim 32 has no support in the specification and claims as originally filed.

The specification does not disclose eluting plasminogen and fibrinogen together. The specification discloses sequentially eluting plasminogen and then fibrinogen, see page 7.

The specification does not disclose the buffers for eluting plasminogen or fibrinogen comprises a salt of citrate, phosphate **and** chloride.

The specification discloses plasminogen was removed by eluting with 15 mM alanine, 20 mM NaHPO4, 0.8M NaCl pH 7.5, but no citrate, see page 18, see page 21, lines 30-31.

Fibrinogen was then elute with a buffer comprising 50 mM arginine, 10 mM trisodium citrate, 50 mM NaCl at pH 7.5, but no phosphate, see page 18, line 11-14 or with 20 mM sodium phosphate, 0.05 M EDTA buffer containing either 250 mM sodium chloride or 500 mM sodium chloride, at pH 7 or buffer comprising 20 mM sodium chloride, 50 mM arginine, 250 mM sodium chloride) or 20 mM sodium phosphate, 200 mM arginine, 250 mM sodium chloride at pH 7.0, see page 23, lines 27-33.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 1, 3 and 24-33 are indefinite because the metes and bounds of what would constitute a "*low concentration* of low molecular weight chelating compound" and "*higher concentration* of the same or different low molecular weight chelating compound cannot be determined. Such is a relative term, and neither the specification nor the claims provide adequate guidance to the interpretation of such terms of "low concentration" and "higher concentration" of same or different competitive chelating compound.

Further, not all "amino acids" are competitive chelating compound. The specification discloses just alanine, leucine, lysine and arginine at concentration greater than 20 mM for eluting fibrinogen while less than 20 mM alanine, leucine and less than or equal to 10 mM lysine for

eluting plasminogen off the copper chelated column from copper charged Toyopearl AF chelate 650 (M).

Specifically, the buffer for eluting fibrinogen comprises 20 mM sodium phosphate, 0.05 M EDTA buffer containing either 250 mM sodium chloride or 500 mM sodium chloride, pH 7 or buffer comprising 20 mM sodium chloride, 50 mM arginine, 250 mM sodium chloride) or 20 mM sodium phosphate, 200 mM arginine, 250 mM sodium chloride at pH 7.0, see page 23, lines 27-33. The specification discloses plasminogen was selectively removed by washing with 15 mM alanine buffer, see page 21, lines 30-31.

With respect to "reduced pH compared to loading solution", the metes and bound of reduced pH cannot be determined because the pH of the loading solution is not recited in the claim. Further, there is no difference between "reduced pH compared to loading solution" in eluting plasminogen versus eluting fibrinogen.

With respect to "reduced ionic strength compared to loading solution", the metes and bound of reduced ionic strength cannot be determined because the ionic strength of the loading solution is not recited in the claim. Further, there is no difference between "reduced ionic strength compared to loading solution" in eluting plasminogen versus eluting fibrinogen.

Claims 3 and 4 have the same issues as claim 1 mentioned above.

Claims 24-33 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 3-5, 24-26 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 90/12803 (published November 1, 1990; PTO 1449) in view of Chaga et al (of record, J Biochem Biophys Methods 49: 313-334, 2001; PTO 892) and WO 95/25748 publication (PTO 1449).

The WO 90/12803 publication teaches a method for separation and purification of various proteins such as fibrinogen which comprises the steps of: loading a solution comprising any protein such as fibrinogen and plasminogen activator and contaminants onto an immobilized metal ion such as such as copper, nickel or zinc affinity chromatography matrix (IMAC) (see entire document, page 14, lines 11-17, claims 1, 9 and 15, page 4, lines 2-23, in particular) and selective eluting the protein of interest such as fibrinogen off the matrix using a buffer comprising higher concentration of weak ligand than the loading solution, i.e., binding buffer that will compete with the fibrinogen for binding to the metal on the basis of the strength of the protein's ability for the metal (see claim 1 step (b), page 15, line 16-10, in particular). The reference eluting buffer for fibrinogen comprises a salt of Tris chloride (see claim 5 of the publication, in particular) or NaCl or KCl (see page 9, line 34-35, in particular). The reference buffer for eluting fibrinogen has a pH of 7.5, which is within the claimed range of 6-8 (see claim 12 of the publication, in particular).

The invention in claim 1 differs from the teachings of the reference only in that the method for separation and purification of fibrinogen by loading a solution comprising fibrinogen and plasminogen and the competitive ligand is imidazole.

The invention in claim 5 differs from the teachings of the reference only in that the method for separation and purification of fibrinogen wherein the solution comprising fibrinogen is a fibrinogen-containing plasma fraction.

The invention in claim 24 differs from the teachings of the reference only in that the method for separation and purification of fibrinogen further comprises the step of concentrating the fibrinogen by ultrafiltration to a concentration of approximately 15 to 30 mg/ml.

The invention in claim 25 differs from the teachings of the reference only in that the method for separation and purification of fibrinogen further comprising the step of combining the fibrinogen with a combination of suitable stabilizers to form a fibrinogen formulation; sterilizing

the fibrinogen formulation by filtration and lyophilizing the fibrinogen the fibrinogen formulation to form a lyophilized fibrinogen formulation.

The invention in claim 26 differs from the teachings of the reference only in that the method for separation and purification of fibrinogen wherein the stabilizers is a detergent.

Chaga et al teach metal ion affinity chromatography matrix chelated with intermediate metal ions such as copper (Cu), Zinc (Zn), Nickel (Ni) are usually eluted by decreasing pH, causing the protonation of the nitrogens of the histidine side chains and consequent disruption of the coordination of bond between the amino acids and the immobilized metal ions, see page 321, last paragraph, page 314, in particular) or competitive chelating compound or displacer such as imidazole (see page 321, last paragraph, in particular). Chaga et al further teach the pH for intermediate metal ions such as copper (Cu), Zinc (Zn), Nickel (Ni) for their optimal adsorption and interaction with different side chains on the protein surface is usually neutral pH (see paragraph bridging pages 314 and 315, in particular). The advantages of immobilized metal ion affinity chromatography (IMAC) for purification of proteins are due to its versatility, high capacity, high recovery, mild loading, mild elution, complete regeneration of column and low cost as taught by Chaga et al (see page 314, Table 1, in particular). IMAC has been extensively use in the successful purification of protein from complex biological samples (see page 315, last paragraph, in particular). Claims 3 and 4 are included in this rejection because the term "or" and Chargas et al teaches metal ion affinity chromatography matrix chelated with intermediate metal ions such as copper (Cu), Zinc (Zn), Nickel (Ni) are usually eluted by *decreasing pH*, causing the protonation of the nitrogens of the histidine side chains and consequent disruption of the coordination of bond between the amino acids and the immobilized metal ions (see page 321, last paragraph, page 314, in particular) or competitive chelating compound or displacer such as *imidazole* (see page 321, last paragraph, in particular).

The WO 95/25748 publication teaches loading a solution such as plasma comprising fibrinogen, factor XIII and plasminogen onto cation affinity column such as lysine affinity column or lysine Sepharose 4B under conditions such that the plasminogen is removed by adsorbing to the lysine sepharose column (see entire document, summary of invention, page 5, page 8, line 9-20, claims 1, in particular). The publication teaches the removal of plasminogen is important because when converted to plasmin, it will break down fibrinogen and fibrin molecules. The latter are formed from interaction between fibrinogen and thrombin in the fibrin sealant to be produced from the composition (see page 8, line 18-22, in particular). The

publication further teaches concentrating the fibrinogen by ultrafiltration to a desired concentration such as 20 mg/ml or less before the step of lyophilized the composition (see page 12, line 20, page 35, line 1, page 18, line 1-5, page 18, line 21-22, in particular). The reference 20 mg/ml or less would include the claimed term of approximately 15 to 30 mg/ml such as 14, 15, 16, 17, 18, 19, and 20 mg/ml. The WO 95/25748 publication further teaches combining the fibrinogen with any suitable stabilizer such as human albumin, and/or a detergent such as polysobate-80 (see page 17, line 26-30, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to separate and purify fibrinogen from other proteins such as plasminogen using immobilized metal ion such as such as copper, nickel or zinc affinity chromatography matrix (IMAC) of the WO 90/12803 publication by loading a solution such as plasma or cryoprecipate that comprises fibrinogen, plasminogen and factor XIII as taught by the WO 95/25748 publication by loading the plasma solution onto a copper immobilized column and then selectively eluting the fibrinogen off the column using a buffer comprising higher concentration of competitive weak ligand such as imidazole than the loading solution or binding buffer as taught by the WO 91/12803 or a solution with decreasing pH as taught by Chaga et al and then concentrating the fibrinogen by ultrafiltration and adding stabilizer such as detergent as taught by the WO 95/25748 publication.

One having ordinary skill in the art would have been motivated to separate fibrinogen from plasminogen because when plasminogen converted to plasmin, it will break down fibrinogen and fibrin molecules as taught by the WO 95/25748 publication.

One having ordinary skill in the art would have been motivated to use decreasing pH and/or imidazole as competitive chelating compound for binding to metal ion column (IMAC) because it is customary in the art to use decreasing pH or imidazole as competitor for eluting or reducing the binding of protein of interest to the intermediate ions such as copper (Cu), Zinc (Zn), Nickel (Ni) immobilized column and collect the fraction that contain the protein of interest as taught by Chaga et al (see page 321, last paragraph, page 314, page 321, last paragraph, in particular)

One having ordinary skill in the art would have been motivated to use immobilized metal ion affinity chromatography (IMAC) because of its versatility, high capacity, high recovery, mild loading, mild elution, complete regeneration of column and low cost as taught by Chaga et al (see page 314, Table 1, in particular). IMAC has been extensively use in the successful purification of

protein from complex biological samples such as plasma (see page 315, last paragraph, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007)* and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

In this case, using known technique of IMAC as taught by the WO 90/12803 publication, and Chaga et al to improve similar products such as purifying fibrinogen and plasminogen in the same way by eluting fibrinogen using decreasing pH or increasing concentration of competitive chelating compound such as imidazole as taught by Chaga et al have been predictable at the time the invention was made, there would have been reasonable expectation of success in combine the references teachings to arrive at the claimed invention.

In this case, applying known technique of IMAC as taught by the WO 90/12803 publication and Chaga et al and then ultrafiltration to concentrate the product and lyophilization as taught by WO 95/25748 publication to a known product such as fibrinogen thereby improving the yield of the product.

An obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007).* From the combined teachings of the references, it is

apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

14. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 90/12803 (published November 1, 1990; PTO 1449) in view of Chaga et al (of record, J Biochem Biophys Methods 49: 313-334, 2001; PTO 892) and WO 95/25748 publication (PTO 1449) as applied to claims 1, 3-5, 24-26 and 31-33 mentioned above and further in view of WO 96/17631 publication (PTO 1449).

The combined teachings of the WO 90/12803, Chaga et al and WO 95/25748 publication have been discussed supra.

The invention in claim 27 differs from the teachings of the references only in that the method for separation and purification of fibrinogen further comprising the step of subjecting the lyophilized fibrinogen formulation to dry heat treatment.

The WO 96/17631 publication teaches lyophilized fibrinogen is heat treated such as at 70 °C to 100°C for up to 96 hours and such heat treatment is more effective in viral inactivation (see page 8, lines 6 through page 10, line 4, page 14, second paragraph, claims 18-19 of the publication, page 18, second full paragraph, in particular). WO 96/17631 publication teaches various stabilizers such as sucrose (carbohydrate, see page 20, second paragraph, in particular) or arginine (amino acid) to protect the formulation during freezing and to stabilize during subsequent heat treatment (see page 13, third paragraph, in particular). The advantage of lyophilized protein has good solubility in water and the benefit of heat-treated lyophilized protein in vial includes viral inactivation and reduced contamination (see page 14, line last two full paragraph, in particular). The typical formulation buffer for fibrinogen is Tris sodium citrate, and sucrose at a pH of 6.8 to 7.6 (see page 16, last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include the step of heat treatment after lyophilization as taught by WO 96/17631 publication for the method of purifying fibrinogen or plasminogen using immobilized metal ion affinity chromatography matrix as taught by the WO 90/12803, Chaga et al and WO 95/25748 publication.

One having ordinary skill in the art would have been motivated to do this because the WO 96/17631 publication teaches the advantage of heat treatment after lyophilization is that it is more effective in viral inactivation (see page 8, lines 6 through page 10, line 4, page 14, second

paragraph, claims 18-19 of the publication, page 18, second full paragraph, in particular); the advantage of lyophilized protein is good solubility in water and the benefit of heat-treated lyophilized protein in vial includes viral inactivation and reduced contamination (see page 14, line last two full paragraph, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

15. Claims 29-30 are free of prior art, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and overcoming the issue of indefinite under 112 second paragraph (claims 29-30).

16. Claim 34 is objected to, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.

19. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
November 20, 2009